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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,928	10/05/1998	NORIO INOMATA	001560-336	8658

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EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/171,928	Inomata et al.
Examiner	**Art Unit**
Michael Borin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 2, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *6, 8-14, and 21-27* is/are pending in the application.

4a) Of the above, claim(s) *21, 23, 25, and 27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *6, 8-14, 22, 24, and 26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *16, 18*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Continued examination under 37 CFR 1.114 after final rejection

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/2/01 has been entered.

Status of Claims

2. Claims 6, 8-14,21-27 are currently pending.

Newly submitted claims 21,23,25,27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 21,23,25,27 are directed to method of treatment of chronic heart failure. Method of treatment of this condition is independent and/or patentably distinct because heart failure can be caused by etiologies unrelated from cardiac hypertrophy (which is the objective of originally presented claims), such as myocardial infarction, cardiomyopathy or chronic hypertension. Consequently, a reference teaching treatment of chronic heart failure may not teach or suggest treatment of cardiac hypertrophy, and *vice versa*.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21,23,25,27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

3. Applicants' Information Disclosure Statements filed 6/22/01 and 8/16/01 have been received and entered into the application. The reference cited in the Information Disclosure Statement filed 8/16/01 has been considered. The reference cited in the Information Disclosure Statement filed 6/22/01 was not considered as it is in Hungarian and no English language translation was provided. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112, second paragraph.

4. Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The base claim, claim 6, is now limited to continuous administration. Claims 12-14 are drawn to different forms of administration - oral (claim 12), intramuscular and subcutaneous administrations

(claim 13) - or to various delivery forms (claim 14).As applicant directs to pages of the specification describing continuous intravenous administration as proof of written description for a continuous administration (see paper #15, page 4, lines 9-10), the term "continuous administration" is read as meaning intravenous administration. Consequently, claims 12-14 are viewed as lacking antecedent basis.

5. Claims 6,22 (and claims dependent thereupon) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear whether the phrase "not based on diuretic and hypotensive effects" relates to the heart weight, cardiac hypertrophy, or to method of treatment the latter. Accordingly, the phrase "amount ... not effective for said diuretic and hypotensive effects" is also not clear.

Discussion of calculations of dosage ranges.

6. Before turning to particular rejections applicable to this application, Examiner wishes to address dosage recalculations presented in the last response. Using single dosage data from the example in the instant specification and data from several publications, applicant asserts that (1) the dosage of 0.1 μg/kg/min in rat corresponds to the level of about 0.5 ng/ml in plasma in rat; (2) that this level in rat plasma

corresponds to 2.1 ng/ml in human, and (3) that the latter human plasma level corresponds to "effective" amount of 0.025μg/kg/min in human. Examiners disagrees, in part, with these conclusions. First, Example 1 discussed by the applicant, describes the situation of preventing cardiac hypertrophy, rather than treating the already developed disorder. For the latter case (which is the situation claimed), specifications describes different ANP level of 426 pg/ml (p. 17, last page). Even if the plasma level shown in the Example 1 of specification (of about 0.5 ng/ml) is considered, this showing is limited for particular time point (7th day of administration). Note that Hayashi reference demonstrates that ANP blood level is not stable in time (see p. 298, Table 6). Further, the same Table demonstrates that the blood level corresponding to the same infusion dosage of ANP varies with gender. As for the discussion of Table 4 in Hayashi reference, this Table is not being considered as the term $C_{ss,}$ to which applicant refers in the argument, is not defined in the otherwise Japanese language text. Second, Examiner objects freely applied recalculations of ANP levels from one species (rat) into another (human). Maeda reference used for such conversion of numbers is not considered as it is published after the filing date of the instant application[1]. Even if the reference had been

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[1]Since enablement sufficiency is determined as of the filing of an application, the disclosure of a later dated publication cannot be relied upon to supplement an insufficient disclosure of a prior filed application. Gould v. Quigg,3 USPQ2d 1302 (Fed. Cir.1987).

considered, there is no showing of linear dependence of infusion dosages *vs* plasma levels, and thus the 0.5 ng/ml in Maeda can not be recalculated into 0.1 μg/kg/min used in humans in Abata so that the latter is then linked to the same 0.1 μg/kg/min dosage in rats used in the instant application. Note also, that all the discussed references address only one agent, ANP, and data on ANP can not be converted into levels of other agents encompassed by the claims. See, e.g., Maeda reference showing that the levels of BNP are different from ANP (p. 817, left column, first full paragraph).

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 6,8-14,22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 6 is amended and new claim 22 is added which introduce new matter as they use the phrase "amount... not effective for said diuretic and hypotensive effects". There is no disclosure in the specification that the agent as claimed does not cause diuretic

and hypotensive effects during treatment of cardiac hypertrophy. Note that prevention and treatment are considered to have an essential difference in the levels of ANP (and like agents) as the already developed hypertrophy stimulates secretion of ANP or BNP (see Espiner, p. 206, first full paragraph). The only showing in specification of the absence of the diuretic and hypotensive effects is presented for the example of use of particular agent, ANP, in the prevention (rather than treatment) of cardiac hypertrophy. There is no indication that diuretic and hypotensive effects are not present during treatment of cardiac hypertrophy, and that such limited scope of action remains the same for other agents acting on guanylate cyclase ANP receptor.

8. Claims 22,24,26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 22 introduces new matter by using the term "amount sufficient to achieve a plasma level of about 0.5 ng/ml. There is no disclosure in the specification that the agent as claimed induces such plasma level during treatment of cardiac hypertrophy (as opposed to prevention illustrated in Example 1).

9. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 26 introduces new matter by using the term "the effective amount is 0.025 μg/kg/min. There is no disclosure in the specification of such dosage used in the treatment of cardiac hypertrophy. As for recalculation of dosages for ANP from rat to human, see discussion above. As for applicant's argument that the description of said dosage can be found in the specification, pages 13,16, this argument is unfounded because said pages indicate slightly similar dosage for glucose infusion, rather than for the agent of the invention.

10. Claims 6,8-14,22,24,26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing cardiac hypertrophy is rats using ANP at dosages which do not cause hypertensive or diuretic effect, does not reasonably provide enablement for (1) treatment of cardiac hypertrophy in rats with ANP at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with ANP in species other than rats at dosages which do not cause diuretic and hypotensive effects; (3)) treatment of cardiac hypertrophy with agents other than ANP and at dosages which do not cause diuretic and hypotensive effects; (4) treatment, in any species and with any agent as claimed,

at plasma levels, such as in claims 22,24,26, or, more specifically, at dosage as claimed in claim 26.

The specification is limited to demonstration of one agent (ANP) and in one type of species (rats). Furthermore, even though Example 2 demonstrates treatment of cardiac hypertrophy, it is not clear, under such conditions, whether diuretic and hypotensive effects are totally not present and how to achieve effect which specifically excludes such mechanisms. Further, see discussion above about recalculations of dosage ranges made by applicant.

Claim Rejections - 35 U.S.C. § 102 and 103.

11. Claims 6,8-10 are rejected under 35 U.S.C. 102(b) as anticipated by Blaine et al. (US Patent 4652549) as evidenced by Espiner[2].

Blaine teaches method of treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) and fragments thereof. See abstract, summary, claims 1-8. The referenced method anticipates the instantly claimed method of treatment of heart

[2]Note that, although the date of the "Espiner" reference is later than the priority date of the instant application, the reference is a review describing studies preceding the instant application; the reference is used merely to demonstrate well known mechanisms of action.

disease based on hypertrophy comprising administration of a substance that acts on natriuretic receptor, guanylyl cyclase A and is able to accelerate production of cGMP. Note, that it is well known that ANF, as well as its analogs stimulate guanylate cyclase A and production of cGMP. See Espiner, p. 205, last paragraph. Therefore, the effects of ANF as instantly claimed are inherently present.

As for the new claim limitation "amount... not effective for diuretic and hypertensive effects", the reference is silent about the presence of such effects of ANP. Demonstration of reduction in water content described in the reference does not amount to demonstration of a diuretic effect as asserted by applicant. Note that prior art acknowledges that, first, natriuretic peptides have a wide range of actions, and, second, hypertrophy is a result of an interaction between a variety of different interrelated signaling pathways. See, for example, Espiner, p. 205, right column, lines 30-33; Hefti, p.2873, summary. Therefore, it is not possible to discern which particular mechanism was engaged in achieving an overall effect of treatment. Even though separate mechanisms might have been demonstrated in specifically designed model conditions, Examiner assumes that the referenced method inherently included the effect as instantly claimed. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on applicant to show that the referenced method did not include the effect

as instantly claimed. As for the analysis of dosage ranges provided by applicant, see the discussion above.

In regard to claim 7, chronic heart failure is a disease based on cardiac hypertrophy.

In regard to claim 10, Espiner teaches that BNP is a functional equivalent of ANP. See p. 205, right column through p. 206, left column.

12. Claims 6,8,9 are rejected under 35 U.S.C. 102(b) as anticipated by Berman et al. (JP 63303998) as evidenced by Espiner[3].

Berman et al. teach treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) analogues which bind to natriuretic receptor. See abstract. The referenced method anticipates the instantly claimed method of treatment of heart disease based on hypertrophy comprising administration of a substance that acts on natriuretic receptor, guanylyl cyclase A and is able to accelerate production of cGMP. Note, that it is well known that ANF, as well as its analogs stimulate guanylate

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[3]Note that, although the date of the "Espiner" reference is later than the priority date of the instant application, the reference is a review describing studies preceding the instant application; the reference is used merely to demonstrate well known mechanisms of action.

cyclase A and production of cGMP. See Espiner, p. 205, last paragraph. Therefore, the effects of ANF analogues as instantly claimed are inherently present.

As for the new claim limitation "amount... not effective for diuretic and hypertensive effects", the reference is silent about the presence of such effects of ANP. Note that prior art acknowledges that, first, natriuretic peptides have a wide range of actions, and, second, hypertrophy is a result of an interaction between a variety of different interrelated signaling pathways. See, for example, Espiner, p. 205, right column, lines 30-33; Hefti, p.2873, summary. Therefore, it is not possible to discern which particular mechanism was engaged in achieving an overall effect of treatment. Even though separate mechanisms might have been demonstrated in specifically designed model conditions, Examiner assumes that the referenced method inherently included the effect as instantly claimed. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on applicant to show that the referenced method did not include the effect as instantly claimed. As for the analysis of dosage ranges provided by applicant, see the discussion above.

13. Claims 6,8-14 are rejected under 35 U.S.C. 103(a) as obvious over Blaine or Berman in view of Cao et al. (Hypertension, 25, 227-234, 1995).

The primary references (as discussed above) teach treatment of cardiac hypertrophy by natriuretic peptides. The primary references do not teach that the reduction of heart weight achieved as a result of the treatment excludes, specifically, such mechanisms as diuretic or hypotensive effects.

Cao et al teaches that (1) Cardiac hypertrophy include stimulation of gene cascade; (2) natriuretic peptides reduce stimulation of this cascade, as evidenced by a decrease in thymidine incorporation. Thus, the reference suggests that "such growth-suppressing activity raise the intriguing possibility that [natriuretic peptides] may function in paracrine fashion to modulate growth in the interstitial compartment during cardiac hypertrophy. See p. 227, bottom. (3) Demonstrates that the hypertrophy-reducing effect of the natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and is further mediated by formation of cGMP (p. 231, and p. 233, second paragraph.

Therefore, it would be obvious to one skilled in the art that cardiac hypertrophy can be reduced by natriuretic peptides by interference with gene activation and that the effect of treating cardiac hypertrophy described in the referenced methods might have included the mechanism as instantly claimed.

14. Claims 6,11-14 are rejected under 35 U.S.C. 103(a) as obvious over Blaine or Berman. The references are applied as above.

If there are any differences between Applicant's claimed methods and that of the prior art, the differences would be appear minor in nature. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ways of administration and pharmaceutical carriers as they are art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art.

Conclusion.

15. No claims are allowed

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER